



## LIFESTAT – Living with statins

### An interdisciplinary project on the use of statins as a cholesterol-lowering treatment and for cardiovascular risk reduction

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### **Rationale for the study**

Millions of individuals worldwide use statins to lower blood cholesterol [1], and perhaps as many as 1 billion worldwide, could be potential candidates for statin treatment. The global market for statins is

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### **Abstract**

**Aim:** LIFESTAT is an interdisciplinary project that leverages approaches and knowledge from medicine, the humanities and the social sciences to analyze the impact of statin use on health, lifestyle and well-being in cohorts of Danish citizens. The impetus for the study is the fact that 10% of the population in the Scandinavian countries are treated with statins in order to maintain good health and to avoid cardiovascular disease by counteracting high blood levels of cholesterol. The potential benefit of treatment with statins should be considered in light of evidence that statin use has prevalent and unintended side effects (e.g. myalgia, and glucose and exercise intolerance). **Methods:** The LIFESTAT project combines invasive human experiments, biomedical analyses, nationwide surveys, epidemiological studies, qualitative interviews, media content analyses, and ethnographic participant observations. The study investigates the biological consequences of statin treatment; determines the mechanism(s) by which statin use causes muscle and mitochondrial dysfunction; and analyzes achievement of treatment goals, people's perception of disease risk, media influence on people's risk and health perception, and the way people manage to live with the risk (personally, socially and technologically). **Conclusions:** **The originality and success of LIFESTAT depend on and derive from its interdisciplinary approach, in which the disciplines converge into thorough and holistic study and describe the impact of statin use on the everyday life of statin users. This has the potential for much greater benefit than any one of the disciplines alone. Integrating traditional disciplines provides novel perspectives on potential current and future social, medical and personal benefits of statin use.**

**Key Words:** *Cholesterol, media, prevention, muscle, myalgia, general practice*

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## Study Design Article

### *LIFESTAT – Living with statins* 535

estimated to be €15 billion, and the Organisation for Economic Co-operation and Development (OECD) recently estimated that no fewer than 91 defined daily doses of statins are consumed per 1000 individuals per day [2]. The average statin user is approximately 60 years old, but this covers a wide age range [3,4]. In the Nordic countries, the number of statin users is high and increasing (Figure 1). About 10% of the population in Scandinavia are treated with statins (Figure 1). In 2014, 612,660 Danes were treated with a statin in the primary sector, and this figure has increased by approximately 20% since 2009, although stagnation was observed in 2012–2013.

Different statins are produced, each chemically a little different from the others, but basically they have the same effect: lowering of total cholesterol, and in particular low-density-lipoprotein cholesterol (LDLC), concentrations in the blood through basically the same mechanism.

The 2012 European guidelines [5] indicate that preventive treatment with statins is appropriate in individuals with >10% predicted risk of a major vascular event within 5 years, while some opinion leaders advocate a 5% threshold [6]. If the guidelines become more liberal, the number of users will probably increase dramatically, and the consequences of this are currently being debated internationally [7].

The downside of statins is the side effects, of which myalgia (muscle pain or aching, stiffness, tenderness or cramps) occurs in 7–29% of statin users [8] and more frequently (> 60%) in physically active athletes [9,10]. Myalgia is a strong disincentive to regular exercise [4,9]. However, a recent study found that statin users in the USA do not take less exercise than a comparable control group [11]. However, as stated in an accompanying editorial [12], a reverse causality may come into play: "...a decrease in exercise levels potentially resulted in adverse physiological and clinical responses, including hypercholesterolemia, which

prompted the initiation of statin therapy, rather than statin therapy reducing the level of habitual physical activity". Thus, the impact of statin therapy on exercise capacity and habits is still an open question.

Regular exercise is one of the critical lifestyle approaches to preventing cardiovascular disease (CVD) and reducing blood cholesterol; any decrease in daily physical activity is a significant negative aspect of statin use. In addition, regular exercise is also effective in preventing and treating obesity and type 2 diabetes, which themselves are risk factors for CVD. Moreover, statin use is linked to increased incidence of type 2 diabetes [13], decreased insulin sensitivity [14], and impaired glucose metabolism and tolerance [15]. Currently, the only way to mitigate statin-induced myalgia is to discontinue treatment with statins, because the mechanistic basis of statin-induced myalgia is poorly understood. Detailed physiological and biochemical information from patients on statins with and without myalgia, during exercise or at rest, is lacking. Also, biomarkers for myalgia are yet to be found. Biomarkers provide a dynamic and powerful approach to understanding the spectrum of side effects of statin treatment.

Defined as alterations in the constituents of tissues or body fluids, these markers offer the means for homogeneous classification of statin risk factors, and they can extend our basic information about the underlying pathogenesis of myalgia.

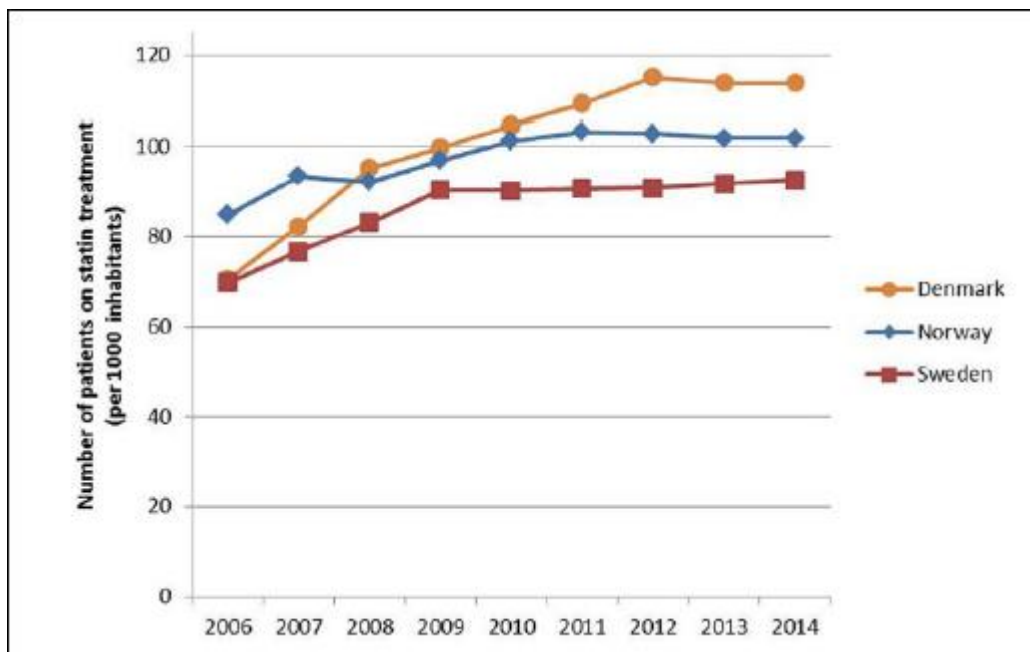


Figure 1. Users of statins (Simvastatin, Lovastatin, Pravastatin, Fluvastatin, Atorvastatin, or Rosuvastatin) 2004–2014 in Denmark, Norway and Sweden prescribed in the primary healthcare sector, users/1000 persons. Sources: Medstat.dk; Reseptregisteret.no; Socialstyrelsen.se.

Statins are effective in reducing blood cholesterol, and some studies with hard end points have indeed shown that statin treatment significantly reduces the frequency of coronary heart disease [16]. Furthermore, the effect of statins is modified by the genetic composition of the individual, such that people with the highest burden of genetic risk derive the largest relative and absolute clinical benefit from statin therapy [17]. In primary prevention, the absolute risk reduction per year for one major vascular event (not necessarily death) ranges from 0.2% to 2.4% in people with a low (<5%) and a high (>30%) 5-year risk, respectively [6]. The corresponding numbers needed to treat range from 500 to 42, respectively. Thus, a relatively large number of people in primary prevention may receive medication throughout life in order to treat a risk factor.

The decision to initiate, maintain and eventually terminate statin treatment is, however, not entirely a decision based upon biomedical knowledge.

However, there are currently no interdisciplinary research missions to explore the complicated interplay between medical knowledge and media discourses on statins vis-à-vis the subjective perception of risk and the individual attitude toward the use of medicine and technology.

The purpose of the present research endeavor, “LIFESTAT – Living with statins”, is to produce new knowledge on this issue, that is, to combine knowledge from medicine, the humanities and the social sciences to analyze the impact of statin use on health, lifestyle and well-being in a cohort of Danish citizens. The vision is that the decision to initiate statin treatment in people and the predominantly biomedical international discussion will be based upon a holistic view of the challenges of statin treatment.

### **Studying the body at risk**

Over the past 50 years, an ever-expanding focus on risk and risk prevention has come to define much of contemporary healthcare in western societies. Thus, the increased prescription of statins can be interpreted as a result of a shift in western societies from looking at “the diseased body” to “the body at risk” [18–20] and from focusing on curative health to also taking into consideration preventive health. This shift is crucial for the way the average citizen views his or her own health status and lives his or her life. The ethnographic part of the LIFESTAT project focuses on the case of increased levels of cholesterol and the use of statins to remedy this condition as an example of a new model of preventive health programming. Using well-established qualitative methods (interviews, focus groups and observations) to study the everyday life of a sub-cohort of 50 individuals, the project will study how this development will impact the everyday life of aging Danes.

Furthermore, qualitative interviews and participant observation will be conducted with participants in the laboratory research that is undertaken for the LIFESTAT project. Parallel with this focus on the

individual (potential) statin user, the study will also examine the mechanisms by which the statistical calculation of risk has come to define health services and their modalities, i.e. through the medication of at-risk conditions. Arguably, prevention is also becoming increasingly commercialized, given that health checks are being offered in workplaces and other environments outside of the clinic, while measurement devices, health gadgets and dietary supplements are on sale from a wide range of suppliers, ranging from supermarkets through hardware stores to pharmacies. Thus, the ethnographic study of statin use in Denmark will include a focus on the individual (potential) statin user, away from questions pertaining to knowledge production in laboratories and toward social, cultural and political complexities of current healthcare.

### **Media influences on statin use and health perception**

Studying people's risk behavior and health perceptions, related in this case to cholesterol and statins, has to take into consideration the fact that media play an important role in affecting people's ideas of health and well-being. Newspapers, television programs and lifestyle magazines as well as websites on the Internet are concerned with topics related to health and disease. The media are a very important source of information and a central way *that* people are informed about health-related issues in general. Equally important, however, is *how* people are informed about health, risk and disease. A comprehensive textual analysis consisting of a quantitative content and a qualitative discourse analysis will be conducted with the aim of studying how the media communicate issues related to cholesterol, statins and health. Using a framing theoretical point of departure [21,22], media content is regarded as decisive for people's knowledge and understanding of things, how they relate to the world, and which opinions they communicate to other people. Thus, media

presentation of cholesterol and statins is an important analytical topic that may influence people's initiative to start or to stop treatment with statins. The basis of this investigation is 3 years' media output relating to statins from two major newspapers and *LIFESTAT – Living with statins* 537 two lifestyle magazines, all based in Denmark ( $n > 700$  articles).

A representative survey instrument has been developed to collect data from 3000 respondents to increase the knowledge of how information on cholesterol and statins is disseminated to the public and how this information influences the individual citizen as patient, pharmaceutical user and personal risk manager. Besides functioning as sources of information and knowledge, the media are an important arena for communication of health issues and hence for decision making. In particular, the Internet has become a popular place both to look for health and medical information and for people to share their experiences with other people [23]. Key questions of the media survey concern *which* media, *when* (before or after people were diagnosed), *how often* people consult media on health issues and on cholesterol, compared with visiting the physician, and *how much time* they spend seeking health information. An important issue is connected to people's evaluation of the reliability of the sources of knowledge. *How do people evaluate* information on cholesterol and statins provided by the media, the physician and health institutions in general: do they find all information equally reliable? Has the possibility of seeking health information on the Internet changed people's relation to the physician and official health institutions, and if so, how? The survey will thus provide an initial picture of *how* people use media as knowledge sources. Finally, the question is whether people feel more secure or whether they become more concerned about their health when media are used as the knowledge source on disease.



### **Media coverage of side effects, information-seeking style and statin use**

As mentioned above, many factors are to be considered when there is a high level of cholesterol in the blood, and there are also many individual ways of handling treatment with statins.

At the same time as statins are being prescribed to an increasing part of the Danish population, during the past 15 years a large proportion of those who are prescribed statins do not redeem prescriptions, and among those who do, about half stop treatment.

General practitioners (GPs) are generally hesitant to stop treatment, and the decision not to take statins is very often made by the individual user, expressed in medical terms as “non-compliance” [24,25].

Information from the media is likely to play a role in this decision. Media set the agenda for which topics are discussed in the general population. The benefits and harms of statins as a risk-reducing drug are discussed among researchers, and this is reflected in the media.

However, information from the media is not passively transferred to the general public; it is also actively sought and processed by the statin user. In this process, socioeconomic status, lifestyle and beliefs about medicines also play a role. From a public health perspective, the LIFESTAT project contributes to the discussion on the use of statins in the general population in two sub-projects.

First, we will use a quasi-experimental design to study whether statin use was affected by a strongly negatively framed newspaper article from 2008. The hypothesis is that those using statins for primary prevention are likely to be more influenced by external factors compared with those using statins after, for instance, a myocardial infarction. The data for this study will be register data for the entire Danish population. Information on prescriptions is available from the Danish National Prescription Database, and information on disease status is available from the national hospital register and use of selected medications.

Further, register data on age, sex and socioeconomic factors are available.

Second, we will focus on factors influencing statin use at the individual level. This study will address the question of how knowledge about cholesterol and statins, information-seeking strategy, lifestyle and beliefs about medicines may influence statin use. We will collect this information from the national survey, and by linking survey data to the Danish National Prescription Database, actual purchases of statins among the survey respondents can be studied. In the survey, we will measure information-seeking style with the Threatening Medical Situations Inventory (TMSI), which classifies individuals on a continuum of two scales: “active seekers” and “information avoiders”. Seeking information on stopping treatment is categorized as being a previous user, and measures of non-adherence include intentional and unintentional non-adherence. The hypothesis is that “active seekers” of information are more likely to be intentional non-adherers, while “information avoiders” are more likely to be unintentional non-adherers. Epidemiological and statistical methods will be used to study associations, taking into consideration the role of educational background, lifestyle and beliefs about medicines.

### **General practice**

In treatment with statins, the individual patient and clinical guidelines are the cornerstones for the decisions by the GP. The guideline defines the goals for treatment and identifies high-risk patients who will benefit from therapy. These treatment goals are based on the present evidence for reducing morbidity and mortality connected to different medical conditions. The goals have been sharpened in recent years, and experts recommend more aggressive treatment with statins [26], although full agreement has not been achieved [27]. Compared with primary prevention, statin therapy is more important in secondary prevention, e.g. for patients suffering from CVD and

diabetes. It is crucial to identify these patients for statin therapy. It is important when planning healthcare to identify groups in the population with special problems in relation to treatment with lipid-lowering drugs. The question is whether the detection of patients for secondary prevention by the healthcare system is influenced by socio-demographic and other individual factors. These issues will be examined using data (diagnosis, level of cholesterol, treatment, disposition and socio-demographic factors) from a population study (The Danish General Suburban Population Study (GESUS)) including 20,876 persons [28]. Another problem in relation to treatment with statins in general practice is side effects, which will be addressed in the following section.

### **Biomedical perspectives**

The mechanism behind statin-induced myalgia is unresolved [8]. Previous studies have shown that myalgic patients on statin treatment are slower to reach peak power output [14], but muscle strength and other measures of muscle performance do not seem to be affected by statin treatment per se [11,29]. However, statins have been shown to have deleterious effects on skeletal muscle mitochondrial function [15], and some authors believe that statin-induced myopathy relates to an inhibitory effect on mitochondrial complex III [30].

Another unwanted side effect of statin treatment is that these drugs increase the risk of type 2 diabetes, and glucose tolerance deteriorates [15]. The mechanism for this effect is also not resolved. One likely scenario could be that the effect of statins on skeletal muscle function paves the way for a vicious circle leading to physical inactivity, which, in turn, will cause diminished insulin sensitivity, weight gain and lack of stimulus for mitochondrial biogenesis. A physically inactive lifestyle combined with obesity will then promote elevation of cholesterol levels. The impact of statin treatment on physical performance, muscle and mitochondrial function as

well as on glucose homeostasis will be studied in ca. 50 patients with and without myalgia and appropriate control subjects. Thorough phenotypic characterization through state-of-the-art methods (glucose clamps, intravenous and oral glucose tolerance tests, muscle power and fitness), including analysis of muscle and adipose tissue biopsies, will pave the way for delineating the mechanism behind statin-induced myalgia and identification of a potential biomarker for myalgia.

### **Potential of the study**

Via the multidisciplinary approach, the present research project will enable a description of the many facets of initiating, maintaining and ending statin treatment in patients with elevated cholesterol levels in the blood. In particular, the factors that determine people's choice to accept or decline medication will be defined, which is of practical clinical use in primary healthcare, where the vast majority of this drug is prescribed. Furthermore, knowledge of the interaction of statins with muscle function will create opportunities for tailored treatment and potential alleviation of the most common side effect, myalgia, which is the primary reason for patients to discontinue treatment. The content analysis of a broad sample of print media output will provide new information on the ways in which knowledge about these issues is disseminated to the public, and the national survey will, for the first time, shed light on the influence of media on people's information-seeking behavior and perception of cholesterol and statin medication. These two media investigations are new within the area of media and communication research, and will contribute significantly to the discussion of what influences people's perception of risk and health in general.

### **Conflict of interest**

The authors declare that there is no conflict of interest.

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